

Appendix A

Scottish mortality data

Approximately 55,000 deaths are registered in Scotland annually (Information Services Division 2016a). Death certificates, completed by a patient's clinician, record cause of death in two free-text sections (Parts 1–2). Part 1 lists the immediate cause of death and works back in time by listing the diseases and conditions that lead to this (Parts 1A–D). Part 2 lists other significant diseases and conditions that contributed to the occurrence of the death (i.e. it is not simply a list of comorbidities) (National Records of Scotland 2020). An automated method of coding, based on a complex set of modification and selection rules, is then used alongside experienced coding staff at NRS to convert the free-text causes of death in Parts 1–2 into their corresponding ICD-10 codes within the NRS death records (National Records of Scotland 2016). NRS arrange these ICD-10 codes into a single primary cause of death field and up to nine secondary cause of death fields. The primary cause of death field contains an ICD-10 code for the underlying cause of death, which is defined as the disease or condition which initiated the chain of morbid events leading directly to death. This can be taken from Part 1 or 2 of the death certificate, according to the modification and selection rules (National Records of Scotland 2016). This final coding process is unique in Scotland because where there are discrepancies in the accuracy of cause of death information in the initial death certificates, NRS specialists make amendments to the cause of death through a process of medical enquiries to the certifying doctor, hospital records, and the Procurator Fiscal. The Procurator Fiscal is a statutory legal official that investigates deaths that are accidental, unexpected, unexplained, sudden or suspicious (including ordering a post mortem, where necessary) (National Records of Scotland 2016). This process of NRS medical enquiries helps insure accuracy within the final NRS electronic death certificate free-text and ICD-10 coding for statistical purposes and research, which are used to develop public health policies (Chief Medical Officer 2018). In a recent review of 6,000 Scottish death certificates (10% of all Scottish death certificates), three percent had incorrect cause of death and required either an amendment or replacement death certificate (Death Certification Review Service 2016).

Appendix B

B1

Broad filtering list of antiepileptic drugs

	Drug Name
1	Acetazolamide
2	Adrenocorticotrophic hormone (incl. Tetracosactide)
3	Carbamazepine
4	Clobazam
5	Clonazepam
6	Diazepam
7	Eslicarbazepine
8	Ethosuximide
9	Felbamate
10	Fosphenytoin
11	Gabapentin
12	Lacosamide
13	Lamotrigine
14	Levetiracetam
15	Lorazepam
16	Mepenzolate bromide
17	Methsuximide
18	Midazolam
19	Nitrazepam
20	Oxcarbazepine
21	Perampanel
22	Phenobarbital
23	Phenytoin
24	Piracetam
25	Pregabalin
26	Primidone
27	Retigabine
28	Rufinamide
29	Sodium valproate
30	Steripentol
31	Sultiame
32	Temazepam
33	Tiagabine
34	Topiramate
35	Vigabatrin
36	Zonisamide

B2*Narrow filtering list of antiepileptic drugs*

	Drug Name
1	Carbamazepine
2	Clobazam
3	Eslicarbazepine
4	Ethosuximide
5	Gabapentin
6	Lacosamide
7	Lamotrigine
8	Levetiracetam
9	Oxcarbazepine
10	Perampanel
11	Phenobarbital
12	Phenytoin
13	Piracetam
14	Primidone
15	Retigabine
16	Rufinamide
17	Sodium valproate
18	Tiagabine
19	Topiramate
20	Vigabatrin
21	Zonisamide

Appendix C

Primary care dataset

GP practices use Vision medical software to build electronic health records (EHRs) for patients in primary care. Within this system, GPs record symptoms, diagnoses and prescriptions using Read codes, which are a coded thesaurus of clinical terms (Fonferko-Shadrach et al. 2017). This makes it possible to track diagnostic primary care NHS data within a data linkage study environment. In the current study, Albasoft Ltd (Albasoft 2020) made contact with all of the GP practices in Scotland and electronically extracted an agreed list of epilepsy-related data variables (see below) from consenting GP practices and transferred them to eDRIS for linkage. Extraction was completed when 100 GP practices were recruited. The study was limited to this number of practices by monetary resource limitations. We extracted all available F25 Read codes and their dates for each participant recruited.

Primary care recruitment diagnostic filtration codes (Fonferko-Shadrach et al. 2017; Pickrell et al. 2015)

<i>Read Code</i>	<i>Description</i>	<i>Event count</i>
<i>F25..</i>	Epilepsy	3151
<i>F2516</i>	Grand mal seizure	469
<i>F25z.</i>	Epilepsy NOS	494
<i>F2510</i>	Grand mal (major) epilepsy	238
<i>F253.</i>	Grand mal status	86
<i>F2514</i>	Epileptic seizures - tonic	67
<i>F2512</i>	Epileptic seizures - clonic	114
<i>F2540</i>	Temporal lobe epilepsy	57
<i>F2515</i>	Tonic-clonic epilepsy	62
<i>F2545</i>	Complex partial epileptic seizure	60
<i>F2500</i>	Petit mal (minor) epilepsy	110
<i>F25X.</i>	Status epilepticus, unspecified	43
<i>F2550</i>	Jacksonian, focal or motor epilepsy	52
<i>F2556</i>	Simple partial epileptic seizure	28
<i>F258.</i>	Post-ictal state	27
<i>F251z</i>	Generalised convulsive epilepsy NOS	26
<i>F251.</i>	Generalised convulsive epilepsy	21
<i>F254z</i>	Partial epilepsy with impairment of consciousness NOS	14
<i>F2513</i>	Epileptic seizures - myoclonic	14
<i>F25B.</i>	Alcohol-induced epilepsy	10
<i>F2503</i>	Epileptic seizures - akinetic	8
<i>F252.</i>	Petit mal status	7
<i>F254.</i>	Partial epilepsy with impairment of consciousness	≤5

<i>F25y.</i>	Other forms of epilepsy	6
<i>F251y</i>	Other specified generalised convulsive epilepsy	11
<i>F25H.</i>	Generalised seizure	≤5
<i>F25y2</i>	Locationally-related (focal) (partial) idiopathic epilepsy and epileptic syndrome with seizures of local onset	≤5
<i>F2502</i>	Epileptic seizures - atonic	≤5
<i>F255.</i>	Partial epilepsy without impairment of consciousness	9
<i>F25y3</i>	Complex partial status epilepticus	6
<i>F2544</i>	Epileptic automatism	≤5
<i>F25yz</i>	Other forms of epilepsy NOS	≤5
<i>F255z</i>	Partial epilepsy without impairment of consciousness NOS	≤5
<i>F256.</i>	Infantile spasms	≤5
<i>F2560</i>	Hypsarrhythmia	≤5
<i>F259.</i>	Early infant epileptic encephalopathy with suppression bursts	≤5
<i>F25F.</i>	Photosensitive epilepsy	≤5
Total		5218

Table 1: Results of Level 1 validation of a single database coding or AED strategy

	Database	Coding algorithm	Participants captured	Sample validated	Epilepsy confirmed	TP	FP	FN	PPV (95% CI)	Sn (95% CI)
1*	PIS	≥1 AED (NL)	22,460	936	614	560	64	54	90% (87–92%)	91% (89–93%)
2	NRS	≥1 G40	2,001	936	614	422	47	192	90% (87–93%)	69% (65–72%)
3	NRS	≥1 G40-41	2,143	936	614	446	70	168	86% (84–89%)	73% (69–76%)
4	SMR01	≥1 G40-41, R56.8	8,239	936	614	450	110	164	80% (77–84%)	73% (70–77%)
5	PIS	≥1 AED (BL)	157,509	936	614	576	149	38	79% (77–82%)	94% (92–96%)
6	Primary care	≥1 F25	1,483	155	120	120	35	NA	77% (70–83%)	NA
7	NRS	≥1 G40-41, R56.8	2,571	936	614	533	243	81	69% (65–72%)	87% (84–90%)
8	NRS	≥1 G41	179	936	614	39	25	575	61% (49–73%)	6% (4–8%)
9	NRS	≥1 R56.8	609	936	614	102	160	512	39% (33–45%)	17% (14–20%)

Key: * = Optimal case-ascertainment strategy(s)

Abbreviations: SMR – Scottish Morbidity Record; PIS – Prescription Information Service; NRS – National Records of Scotland; AED – antiepileptic drug; F25 – primary care diagnostic Read Codes for epilepsy; G40–41 – International Classification of Disease 10 (ICD-10) codes for epilepsy and status epilepticus; R56.8 – ICD-10 code for seizures; NL – AEDs on the narrow list (appendix S2b); BL – AEDs on the broad list (appendix S2a); TP – true positive; FP – false positives; FN – false negatives, PPV – positive predictive value; Sn – sensitivity; CI – confidence intervals; NA – not applicable (negative cases unavailable as primary care data were taken from a 10% sample of Scottish GP practices)

Table 2: Results of Level 2 validation of algorithms combining two database coding or AED strategies together

	Database	Coding algorithm	Participants captured	Sample validated	Epilepsy confirmed	TP	FP	FN	PPV (95% CI)	Sn (95% CI)
1	Primary care + NRS	≥1 F25 + ≥1 R56.8	13	155	120	8	0	112	100% (100–100%)	7% (2–11%)
2	NRS + PIS	≥1 G40-41 + ≥1 AED (NL)	1781	936	614	419	28	195	94% (92–96%)	68% (65–72%)
3	NRS + PIS	≥1 G40 + ≥1 AED (NL)	1732	936	614	402	26	212	94% (92–96%)	66% (62–69%)
4	SMR01 + PIS	≥1 G40-41, R56.8 + ≥1 AED (NL)	6501	936	614	418	34	196	93% (90–95%)	68% (64–72%)
5	NRS + PIS	≥1 G40 + ≥1 AED (BL)	1798	936	614	407	31	207	93% (91–95%)	66% (63–70%)
6	SMR01 + NRS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G40	1167	936	614	325	23	289	93% (91–96%)	53% (49–57%)
7*	NRS + PIS	≥1 G40-41, R56.8 + ≥1 AED (NL)	1921	936	614	494	47	120	91% (89–94%)	81% (77–84%)
8	NRS + PIS	≥1 G40-41 + ≥1 AED (BL)	1883	936	614	426	42	188	91% (88–94%)	69% (66–73%)
9	SMR01 + PIS	≥1 G40-41, R56.8 + ≥1 AED (BL)	7227	936	614	424	48	190	90% (87–93%)	69% (65–73%)
10	Primary care + NRS	≥1 F25 + ≥1 G40-41, R56.8	199	155	120	68	8	52	90% (83–96%)	57% (48–66%)
11	SMR01 + NRS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G40-41	1273	936	614	347	42	267	89% (86–92%)	57% (53–60%)
12	Primary care + NRS	≥1 F25 + ≥1 G40-41	192	155	120	63	8	57	89% (81–96%)	53% (44–61%)
13	Primary care + NRS	≥1 F25 + ≥1 G41	8	155	120	X	X	X	89% (81–96%)	53% (44–61%)
14	Primary care + NRS	≥1 F25 + ≥1 G40	188	155	120	62	8	58	89% (81–96%)	52% (43–61%)
15	NRS + PIS	≥1 G41 + ≥1 AED (NL)	81	936	614	X	X	X	88% (77–99%)	5% (3–7%)
16*	Primary care + PIS	≥1 F25 + ≥1 AED (NL)	1089	155	120	111	18	9	86% (80–92%)	93% (88–97%)
17	Primary care + SMR01	≥1 F25 + ≥1 G40-41, R56.8	613	155	120	85	15	35	85% (78–92%)	71% (63–79%)
18	NRS + PIS	≥1 G40-41, R56.8 + ≥1 AED (BL)	2107	936	614	507	98	107	84% (81–87%)	83% (80–86%)
19	SMR01 + NRS	≥1 G40-41, R56.8	1390	936	614	386	76	228	84% (80–87%)	63% (59–67%)
20	NRS + PIS	≥1 R56.8 + ≥1 AED (NL)	281	936	614	89	17	525	84% (77–91%)	15% (12–17%)
21	Primary care + PIS	≥1 F25 + ≥1 AED (BL)	1255	155	120	112	27	8	81% (74–87%)	93% (89–98%)
22	NRS + PIS	≥1 G41 + ≥1 AED (BL)	117	936	614	32	13	582	71% (58–84%)	5% (4–7%)
23	SMR01 + NRS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 R56.8	220	936	614	58	30	556	66% (56–76%)	9% (7–12%)

24	NRS + PIS	≥1 R56.8 + ≥1 AED (BL)	403	936	614	95	52	519	65% (57–72%)	16% (13–18%)
25	SMR01 + NRS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G41	139	936	614	36	21	578	63% (51–76%)	6% (4–8%)

Key: * = Optimal case-ascertainment strategy(s); X – categories with five or less events hidden to protect patient identity

Abbreviations: SMR – Scottish Morbidity Record; PIS – Prescription Information Service; NRS – National Records of Scotland; AED – antiepileptic drug; F25 – primary care diagnostic Read Codes for epilepsy; G40–41 – International Classification of Disease 10 (ICD-10) codes for epilepsy and status epilepticus; R56.8 – ICD-10 code for seizures; NL – AEDs on the narrow list (appendix S2b); BL – AEDs on the broad list (appendix S2a); TP – true positive; FP – false positives; FN – false negatives, PPV – positive predictive value; Sn – sensitivity; CI – confidence intervals

Table 3: Results of Level 3 validation of algorithms combining three database coding or AED strategies together

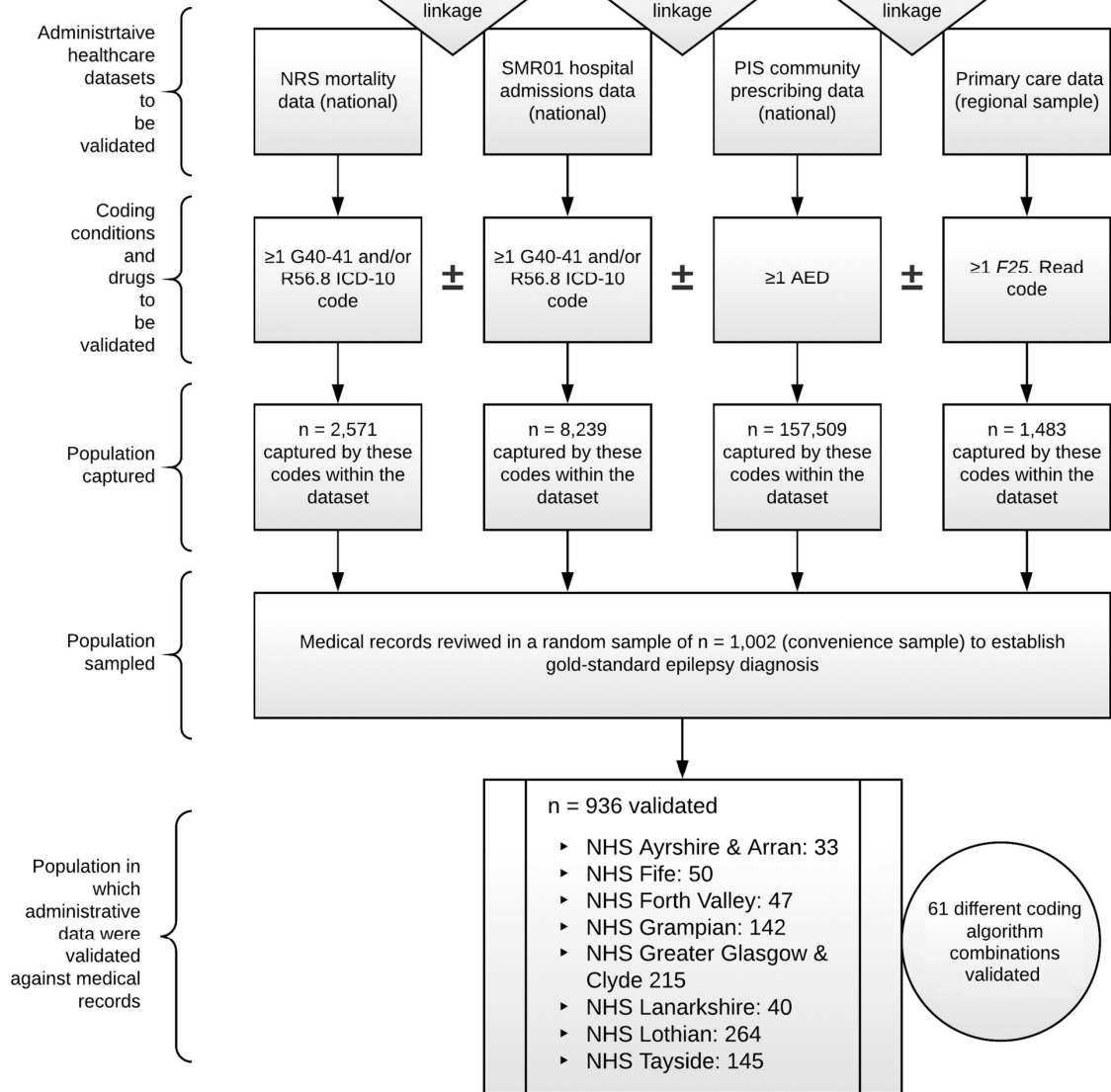
	Database	Coding algorithm	Participant s captured	Sample validated	Epilepsy confirme d	TP	F P	FN	PPV (95% CI)	Sn (95% CI)
1	Primary care + NRS + PIS	≥1 F25 + ≥1 R56.8 + ≥1 AED (BL)	11	155	120	7	0	11 3	100% (100– 100%)	6% (2–10%)
2	Primary care + NRS + PIS	≥1 F25 + ≥1 R56.8 + ≥1 AED (NL)	11	155	120	7	0	11 3	100% (100– 100%)	6% (2–10%)
3	Primary care + SMR01 + NRS	≥1 F25 + SMR01 ≥1 G40-41, R56.8 + NRS ≥1 R56.8	11	155	120	7	0	11 3	100% (100– 100%)	6% (2–10%)
4	Primary care + NRS + PIS	≥1 F25 + ≥1 G41 + ≥1 AED (BL)	8	155	120	X	X	X	100% (100– 100%)	3% (0–5%)
5	Primary care + NRS + PIS	≥1 F25 + ≥1 G41 + ≥1 AED (NL)	8	155	120	X	X	X	100% (100– 100%)	3% (0–5%)
6	Primary care + SMR01 + NRS	≥1 F25 + SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G41	7	155	120	X	X	X	100% (100– 100%)	2% (0–4%)
7	SMR01 + NRS + PIS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G40-41 + ≥1 AED (NL)	1119	936	614	32 8	19	28 6	95% (92–97%)	53% (50– 57%)
8	SMR01 + NRS + PIS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G40 + ≥1 AED (BL)	1101	936	614	31 4	17	30 0	95% (93–97%)	51% (47– 55%)
9	SMR01 + NRS + PIS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G40 + ≥1 AED (NL)	1075	936	614	31 4	17	30 0	95% (93–97%)	51% (47– 55%)
10	SMR01 + NRS + PIS	≥1 G40-41, R56.8 + ≥1 AED (NL)	1185	936	614	36 6	26	24 8	93% (91–96%)	60% (56– 64%)
11	SMR01 + NRS + PIS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G40-41 + ≥1 AED (BL)	1168	936	614	33 1	26	28 3	93% (90–95%)	54% (50– 58%)
12	SMR01 + NRS + PIS	≥1 G40-41, R56.8 + ≥1 AED (BL)	1247	936	614	37 0	38	24 4	91% (88–94%)	60% (56– 64%)
13	Primary care + SMR01 + PIS	≥1 F25 + ≥1 G40-41, R56.8 + ≥1 AED (NL)	555	155	120	79	9	41	90% (83–96%)	66% (57– 74%)
14	SMR01 + NRS + PIS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 R56.8 + ≥1 AED (NL)	156	936	614	56	6	55 8	90% (83–98%)	9% (7–11%)
15	Primary care + NRS + PIS	≥1 F25 + ≥1 G40-41, R56.8 + ≥1 AED (BL)	195	155	120	66	8	54	89% (82–96%)	55% (46– 64%)
16	Primary care + NRS + PIS	≥1 F25 + ≥1 G40-41, R56.8 + ≥1 AED (NL)	194	155	120	66	8	54	89% (82–96%)	55% (46– 64%)
17	Primary care + SMR01 + NRS	≥1 F25 + ≥1 G40-41, R56.8	115	155	120	48	6	72	89% (81–97%)	40% (31– 49%)

1 8	Primary care + NRS + PIS	≥1 F25 + ≥1 G40-41 + ≥1 AED (BL)	188	155	120	61	8	59	88% (81–96%)	51% (42–60%)
1 9	Primary care + NRS + PIS	≥1 F25 + ≥1 G40-41 + ≥1 AED (NL)	187	155	120	61	8	59	88% (81–96%)	51% (42–60%)
2 0	Primary care + NRS + PIS	≥1 F25 + ≥1 G40 + ≥1 AED (BL)	184	155	120	60	8	60	88% (81–96%)	50% (41–59%)
2 1	Primary care + NRS + PIS	≥1 F25 + ≥1 G40 + ≥1 AED (NL)	183	155	120	60	8	60	88% (81–96%)	50% (41–59%)
2 2	Primary care + SMR01 + NRS	≥1 F25 + SMR01 ≥1 G40-41, R56.8 + NRS G40-41	111	155	120	45	6	75	88% (79–97%)	38% (29–46%)
2 3	Primary care + SMR01 + NRS	≥1 F25 + SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G40	107	155	120	44	6	76	88% (79–97%)	37% (28–45%)
2 4	SMR01 + NRS + PIS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G41 + ≥1 AED (NL)	73	936	614	X	X	X	88% (76–99%)	5% (3–6%)
2 5	Primary care +SMR01 + PIS	≥1 F25 + ≥1 G40-41, R56.8 + ≥1 AED (BL)	577	155	120	80	11	40	85% (78–92%)	71% (63–79%)
2 6	SMR01 + NRS + PIS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 R56.8 + ≥1 AED (BL)	175	936	614	57	11	55 7	84% (75–93%)	9% (7–12%)
2 7	SMR01 + NRS + PIS	SMR01 ≥1 G40-41, R56.8 + NRS ≥1 G41 + ≥1 AED (BL)	96	936	614	29	11	58 5	73% (59–86%)	5% (3–6%)

Key: X – categories with five or less events hidden to protect patient identity

Abbreviations: SMR – Scottish Morbidity Record; PIS – Prescription Information Service; NRS – National Records of Scotland; AED – antiepileptic drug; F25 – primary care diagnostic Read Codes for epilepsy; G40–41 – International Classification of Disease 10 (ICD-10) codes for epilepsy and status epilepticus; R56.8 – ICD-10 code for seizures; NL – AEDs on the narrow list (appendix S2b); BL – AEDs on the broad list (appendix S2a); TP – true positive; FP – false positives; FN – false negatives, PPV – positive predictive value; Sn – sensitivity; CI – confidence intervals

1A



1B

